Gastric mucosal disease
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Chapter 2

Helicobacter Pylori Gastritis -

A Global View

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**ABSTRACT**

*Background and Aim:* *H. pylori* is an etiologic component of chronic gastritis and other gastroduodenal diseases. Its prevalence varies widely in different parts of the world. There are significant geographical differences between its prevalence and clinical manifestation. The aim of this study was therefore to compare gastric mucosa in various age cohorts of *H. pylori*-infected dyspeptic individuals from several geographical areas in the world using a standardized grading system. In addition the prevalence of atrophy and intestinal metaplasia were compared with the respective gastric cancer incidence.

*Methods:* Totally 1991 patients infected with *H. pylori* attending the eleven gastroenterological clinics from nine countries were selected for this study. Hematoxylin-eosin stained biopsies from antrum and corpus were scored semiquantitatively according to a modified updated Sydney system. Particular attention was paid to the degree of glandular atrophy and Intestinal metaplasia (IM) in gastric mucosal biopsies. Box and whiskers plots were used to show the median severity of atrophy and intestinal metaplasia in the various cohorts. The statistical evaluation was done using Kruskal-Wallis test and Spearman's rank correlation test.

*Results:* Analysis of the general median severity of atrophy in the different groups of patients showed significant differences in the antral mucosa. The highest scores of antral atrophy were found in Japan and among New Orleans blacks, and slightly lower in Colombia. Lower scores were seen in China. The lowest scores were found in four European countries and especially in Thailand. As for IM, the scores were low in general except for Xi-an, Japan and Shanghai.
Conclusion: Our findings indicate that there are major geographical differences in the overall prevalence and severity of *H. pylori* gastritis features—atrophy and IM according to age.

These differences mirror the respective incidences of gastric cancer in those geographical areas.
INTRODUCTION

Since its rediscovery in the stomach by Warren and Marshall in 1983, *Helicobacter pylori* has been the focus of a great number of studies from all over the world. These studies have substantially contributed to our understanding of the role of *H. pylori* in gastroduodenal diseases. Overwhelming evidence has implicated this infection as an etiologic component of chronic gastritis, peptic ulcer, and gastric cancer. *H. pylori* infection is considered the leading cause of gastric mucosal inflammation. Chronic inflammation ultimately leads in some individuals to atrophic changes and intestinal metaplasia. The latter condition may predispose to gastric malignancy. The processes that govern the development of atrophy and intestinal metaplasia are complex. Duration of chronic active inflammation together with environmental factors may be of major importance in explaining differences in speed of developments between various geographical areas.

Gastric cancer is the most ominous outcome of *H. pylori* infection. Many experts feel that population screening for *H. pylori* infection should be considered if efficacious, *H. pylori*-specific, well tolerated and safe antimicrobial therapy became available. The optimal timing for such theoretical population screening would obviously depend on the onset and speed of worsening of gastric inflammation, atrophy, intestinal metaplasia and dysplasia. Many investigations have studied gastric mucosal morphology as a function of age. However, comparing the results of those studies turns out to be hazardous, if not impossible, because of lack of uniform definitions and criteria for grading gastric atrophy or intestinal metaplasia. There are several classifications for chronic gastritis: morphological; topographical; and combined morphological and topographical. The discovery of *H. pylori* as a major cause of gastritis has led many investigators to incorporate etiology in the classification of
chronic gastritis\textsuperscript{18-20}. Based on this reason, the Sydney system of classification of chronic gastritis was created at the 9\textsuperscript{th} World Congress of Gastroenterology in Sydney in 1990\textsuperscript{21} and updated at Houston International Gastritis Workshop in 1994\textsuperscript{22-23} to attempt to reach a consensus in grading gastritis. A systematic study of gastric biopsies in \textit{H. pylori}-infected individuals using the latest Houston modification of the Sydney classification system by the same pathologists has not yet been carried out. The aim of this study was therefore to compare gastric mucosa in various age cohorts of \textit{H. pylori}-infected dyspeptic individuals from several geographical areas in the world using a standardized grading system, in order to compare the degrees of atrophy and intestinal metaplasia according to age. In addition, the prevalence of atrophy and intestinal metaplasia was compared to respective gastric cancer incidences in those geographical areas.
MATERIALS AND METHODS

Study populations

In this study total 2043 patients with ulcer or non-ulcer dyspepsia attending eleven gastroenterological clinics from nine countries were investigated. Only patients with \textit{H. pylori} infection proven by rapid urease test were included. Exclusion criteria were age less than 18 or greater than 75 years, history of gastrectomy, active upper gastrointestinal bleeding or perforation and severe gastro-oesophageal reflux disease. Patients receiving analgesic medication or drugs with a possible effect on \textit{H. pylori} were excluded.

According to the geographic area, the total cohort consisted of eleven groups. 291 Dutch patients from Academic Medical Center, University of Amsterdam, a total of 756 Chinese cases from the university hospital in three cities of China—Guangzhou, Shanghai and Xi-an were included in multinational follow-up studies (Dutchigas \textit{Hp} project) on \textit{H. pylori} eradication therapy in Netherlands and China; 35 Colombian patients from the area of Narino, in the rural south Andes (Colombia) who were participants in a chemoprevention trial intended to last 6 years; 50 American patients from GI clinic of Louisiana State University Medical Center (New Orleans, USA), with 43 Black and 7 White patients; 105 patients from Helsinki University Central Hospital (Helsinki, Finland); 524 Thailand patients from Siriral Hospital (Bangkok, Thailand); 257 Germany cases from Institute of Pathology Bayreuth (Bayreuth, Germany); 250 Portuguese patients from Hospital de S.Joao (Porto, Portugal); and 282 Japanese cases from Kure Kyosai Hospital and Tohoku University School of Medicine (Kure and Seidai, Japan). Patients were excluded from analysis if some parameters were missing or incomplete and if patients turned out to be \textit{H. pylori} negative by histopathologic examination. All the results (tables and Figures) were based on those cases
with complete information for the parameter under study, excluding those with missing values and *H. pylori* negative cases. General information concerning the patients are summarized in Table 1.

Patients were divided into five different age categories: less than 30 years, 31-40 years, 41-50 years, 51-60 years and over 60 years.

**Study protocol**

Upper gastrointestinal endoscopy was performed on all the patients after an overnight fast.

At least two biopsy specimens were taken from the antrum within 2-3 cm from the pylorus in *H. pylori* positive individuals. Two corpus biopsies also taken of the lesser and greater curve, some 10 cm from the cardia, except in the Netherlands and Xi-an. From the group of New Orleans, Colombia and Thailand, one antrum and one corpus biopsies was obtained.

Additional biopsy specimens were taken from any lesions in all cases.

Biopsy specimens were fixed in 10% formalin and then processed, embedded in paraffin, cut in sequential 4 μm sections and routine stained with hemotoxylin-eosin (H&E). Additional Gent stain was performed in the cases with doubtful identification of *H. pylori*. When *H. pylori* was absent in both H&E and Gent stained slides, the patient was categorized as *H. pylori* negative. Virtually all available specimens included surface epithelium and muscularis mucosae.

**Histopathology**

All sections were interpreted independently by a single especially trained and experienced pathologist (YL), who was unaware of the clinical or endoscopic finding.

Histological sections were evaluated and graded for the following parameters: *H. pylori* colonization, chronic inflammation and inflammatory activity, atrophy, intestinal metaplasia.
A detailed histopathological classification was used in order to allow registration of minor variation in all above features. Therefore the categories 'mild', 'moderate' and 'severe' as used in the updated Sydney system were each subdivided into two further subcategories to allow some fine-tuning, therefore a 1-6 scale was applied: 1-2 (mild), 3-4 (moderate), 5-6 (severe), corresponding to the updated Sydney system.

The density of *Hp* colonisation was graded as follows: 0: none; 1: *Hp* found only in one place after a careful search; 2: only a few *Hp* found; 3: scattered *Hp* found in separated areas/foci; 4: numerous *Hp* in separated areas/foci; 5: nearly complete gastric surface covered by a layer of *Hp*; 6: continuous gastric surface coverage by a thick layer of *Hp*.

Degree of Chronic inflammatory infiltration was scored as follows: 0: absent; 1: scattered chronic inflammatory cells, less than 10 in each high power field; 2: scattered, but more than 10 in each high power field; 3: some areas with dense chronic inflammatory cells; 4: diffuse infiltration with dense chronic inflammatory cells; 5: nearly the whole mucosa containing dense chronic inflammatory cells which separate the gastric glands; 6: entire mucosa containing a dense chronic inflammatory cell infiltration.

For activity of gastritis, the density of neutrophils infiltration of crypts corresponds to the following numbers: 0: absent; 1: involvement of only one crypt per biopsy; 2: involvement of two crypts per biopsy; 3: involvement of many crypts up to 25%; 4: involvement of 25%-50% of the crypts; 5: more than 50% of the crypts are involved; 6: all crypts are involved.

Atrophy was defined as the loss of specialized gastric glandular tissue, with or without replacement by intestinal-type epithelium. Grade 1 equals focally few gastric glands lost or replaced by intestinal-type epithelium; grade 2 equals small areas of gastric glands disappearing or replaced by intestinal-type epithelium; 3 corresponds to 25% gastric glands lost or replaced by intestinal-type epithelium; 4 corresponds to 25-50% of gastric glands lost or replaced by intestinal epithelium; 5 corresponds to more than 50% of gastric glands lost or
replaced by intestinal epithelium; 6 is diagnosed when only a few areas of gastric glands are remaining.

Intestinal metaplasia (IM) was diagnosed when gastric foveolar and glandular epithelium was focally or diffusely replaced by intestinal-type epithelium. It was graded according to the following numbers: 0: absent; 1: present in only one crypt; 2: in one focus (1-4 crypts) in one or both specimens; 3: in two separate foci; 4: multifocal in one or both specimens; 5: more than 50% of crypts are diffusely replaced by intestinal-type epithelium; 6: only a few parts of gastric epithelium are left, not replaced by intestinal epithelium. Complete and incomplete IM were not further differentiated, since mucin histochemical studies were not performed.

The mean degree of gastritis in the antrum was taken as the grade of antral gastritis; the corpus gastritis grade was obtained analogously. The mean grades of inflammatory cells, atrophy and metaplasia were taken as the respective grades to represent the antrum and corpus.

**Statistical analysis:**

Calculations were performed using the SPSS software package, for Windows version 11 (SPSS inc. Chicago, IL, USA). The overall results of the biopsies were expressed as ‘box and whiskers’ plots. Distribution of atrophy and intestinal metaplasia was compared using Kruskal-Wallis test between countries and between different age-groups, age-group also was compared across countries using Kruskal-Wallis test. Spearman’s rank correlation test was used to investigate the correlation between the prevalence of antrum atrophy/IM and gastric cancer incidence, the prevalence of atrophy/IM and age, and prevalence of atrophy and IM. Significance was set at P<0.05.
RESULTS

A total of 1991 *H. pylori*-infected subjects, who underwent gastroscopy for upper gastrointestinal complains, and for whom all data were complete, were analyzed.

The medians and range of all features of *Hp* gastritis were measured in relation to the gender distribution. There were no significant differences between male and female patients (P<0.05).

The overall results of antrum biopsies expressed as 'box and whiskers' plots, both for degrees of atrophy and intestinal metaplasia are summarized in Figures 1 and 2.

An analysis of the median of antrum atrophy (Figure 1) in the different groups of patients showed statistically significant differences in the antral mucosa (P<0.01). Among 1991 investigated *H. pylori* infected individuals, the highest scores were found in Japan (JP) and among New Orleans blacks (NO), and slightly lower scores in Colombia (CA). Lower scores were seen in China –Guangzhou(GU), Shanghai (SH) and Xi-an (XI). The lowest scores were found in Europe: Finland (FI), Netherlands (NL), Germany (GE), Portugal (PO) and especially in Thailand (TH). Degree of atrophy in corpus biopsies were low throughout in all countries and the data are not shown.

On looking more closely at the age distribution in all groups, it also got the significant statistic difference (P<0.01). The median of antrum atrophy below 50 years showed a similar variation: being higher in the subgroup of patients in New Orleans, Japan, Colombia, Xi-an, Shanghai and Guangzhou, except no case in Colombia and too limited number in Finland.

The median degree of atrophy rose with increasing age of the patients in almost all groups and was the highest in the age group above 60 years, despite the Portugal group which got the highest in the age group of 51- 60 years (Table 2).
The severity of the intestinal metaplasia scores in the antrum was in general low except for Xi-an, Japan and Shanghai (Figure 2). Intestinal metaplasia in corpus biopsies was negligible throughout.

The distribution of IM in relation to the age in *H. pylori* associated gastritis is shown in Table 3. Analysis of different age groups revealed that the median IM in Xi-an is the highest in all age groups. With increasing age, the median rose in all groups.

The prevalence of antrum atrophy and intestinal metaplasia were compared to gastric cancer incidence in Table 2 and 3; Figure 3 and 4. For antrum atrophy the correlation was 0.527 (p=0.096). For antrum intestinal metaplasia the correlation was 0.708 (p=0.015). The degree of antrum intestinal metaplasia correlated significantly with antrum atrophy with a correlation coefficient of 0.75 (P<0.01) (Table 4). The age was compared with the prevalence of atrophy and IM with the correlation coefficient of 0.18 and 0.19, respectively (P<0.01).
DISCUSSION

Analysis of random biopsies, particularly from the antrum from consecutive \textit{H. pylori} -infected dyspeptic patients with/without ulcer diathesis, reveals substantial geographical differences in age-related degree of atrophy and intestinal metaplasia. The atrophic/metaplastic changes were largely limited to the antrum and much less pronounced in corpus biopsies. The overall prevalence of atrophy and intestinal metaplasia mirrored the respective incidence of gastric cancer. This finding strengthens the hypothesis that chronic \textit{H. pylori}-associated inflammation is a key factor in gastric carcinogenesis\textsuperscript{25-27}. The observation that atrophy and intestinal metaplasia appeared at younger ages in populations at high risk for gastric cancer than in population at low risk supports the results of many other studies. Particularly striking was the very low prevalence of atrophy and intestinal metaplasia in Thailand, corresponding to a very low gastric cancer incidence. Our findings are in line with the results of Imai et al group\textsuperscript{28-29} who found that atrophy and IM were detected at much earlier ages in Japan than in the USA. The Japanese show a much higher prevalence of \textit{H. pylori} beginning at a much earlier age. This is in accord with the well-known high prevalence of gastric carcinoma in Japan. The shorter duration of infection in population living in the European countries may be one reason why the rates of gastric carcinoma are decreasing. Studies from Finland indicate that the age-specific prevalence of chronic atrophic gastritis in both sexes decreased significantly during the 15 years periods between 1977 and 1992\textsuperscript{30}. This closely mirrors the time trends for gastric carcinoma.

Our study has strengths and weaknesses. Strengths of the study relate to the blind character of the biopsy analysis by the same histopathologist, well trained in the analysis of gastric mucosal biopsies and with an acceptable internal reproducibility. All biopsies were
essentially obtained within the same time frame. All biopsies had pathological proof of

*H. pylori* infection.

Weakness of the study relate to the lack of characterization of the infecting organisms (Cag°, Vac°, Ice A° status unknown); lack of information on percentage with ulcer diathesis, smoking, etc; lack of further characterization of the type of intestinal metaplasia; lack of correlation of gastric mucosal status with gastric secretory function (pepsinogens, gastrins etc); and the occasional low number of biopsies in certain age categories. Particularly the cytotoxin-associated gene A (cag A) seems highly associated with atrophic gastritis and gastric adenocarcinoma, at least in certain but not all countries.

Despite these shortcomings our study clearly shows that there are major geographical differences in the overall prevalence of atrophy and intestinal metaplasia. Duration of chronic active inflammation is obviously an important element. High infection rate very early in life may largely explain the geographical differences in age-related atrophy and metaplasia. In addition environmental factors may also influence the velocity of development of atrophy and metaplasia. Hu et al came to a similar conclusion when they compared the degree of gastric mucosal atrophy in Lan Zhou (high gastric cancer incidence) versus Guangzhou (low gastric cancer incidence). We do not know whether those putative environmental factors require the presence of *H. pylori*, or what those environmental factors are (lack of antioxidants in food? Smoking? Alimentary nitrosamines?). It is now generally accepted that *H. pylori* associated chronic gastritis is a long lasting disease which in the presence of other factors, may in some cases progress to atrophic gastritis and IM. This indicates that atrophic gastritis and IM are late sequel of *Hp* infection and that the pathogenesis of gastric cancer may also be related to *Hp* infection. Although the etiology of gastric cancer is multifactoral, its genesis is almost always preceded by chronic gastritis, and by atrophic gastritis and IM in particular. From the global scale, the highest incidence of gastric cancer is found in Asia
(Japan and China), and in central America and south America (especially the Andean
countries) 77. There exists important geographic differences. Our findings are in agreement
with and may give it the strong support.
We were rather surprised to find that atrophy and metaplasia were largely restricted to the
antrum and almost absent from the corpus biopsies, even in countries with high gastric cancer
prevalence. We cannot rule out that this is caused by the selection of patients with dyspeptic
symptoms or with ulcer diathesis, where inflammation is known to be largely antrum-
predominant. Caution should be taken not to extrapolate our findings to the general non-
symptomatic population in the various geographical areas. Yet in dyspeptics, atrophy and
intestinal metaplasia are more common in the antrum and angular area 36.
Cost calculations have been made in the literature with respect to population screening and
antimicrobial therapy 37. In those studies, screening is projected to start at age 50. It would
appear from our study that a substantial proportion of the (dyspeptic) population already has
variable degrees of atrophy and intestinal metaplasia, especially in countries with high gastric
cancer incidence. If ever population screening became feasible, determination of the most
appropriate starting age would need to be determined, and may well be earlier, especially in
areas with high gastric cancer risk, in order not to pass the 'point of no return' in the
Acknowledgments

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Dr. Kanit Atisook, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Dr. Udom Kachintorn, Siriraj Hospital, Mahidol University, Bangkok, Thailand
REFERENCES


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SD = standard deviation
Figure 1. Box and whiskers plots showing the median severity of antrum atrophy in *H. pylori*-infected individuals. The box extends from the 25th percentile to the 75th percentile with a horizontal line at the median (50th percentile). Whiskers extend down the smallest value and up to the largest
Figure 2. Box and whiskers plot showing the severity of antrum intestinal metaplasia in *H. pylori* -infected individuals.
Table 2. Antrum atrophy (any degree)

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<th>41-50(%)</th>
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* Gastric cancer incidence per 100 000.
Table 3. Antrum intestinal metaplasia (any degree)

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* Gastric cancer incidence per 100 000.
Table 4. Correlation between antrum score for atrophy and intestinal metaplasia

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<td>Guangzhou (GU)</td>
<td>1(0-2)</td>
<td>0(0-0)</td>
<td>0.396</td>
<td>0.11</td>
</tr>
<tr>
<td>Shanghai (SH)</td>
<td>1(0-3)</td>
<td>0(0-2)</td>
<td>0.705</td>
<td>0.14</td>
</tr>
<tr>
<td>New Orleans (NO)</td>
<td>3(1-4)</td>
<td>0(0-0)</td>
<td>0.237</td>
<td>0.09</td>
</tr>
<tr>
<td>Thailand (TH)</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>0.692</td>
<td>0.14</td>
</tr>
<tr>
<td>Portugal (PO)</td>
<td>0(0-2)</td>
<td>0(0-1)</td>
<td>0.943</td>
<td>0.17</td>
</tr>
<tr>
<td>Colombia (CA)</td>
<td>2(0-4)</td>
<td>0(0-1)</td>
<td>0.486</td>
<td>0.70</td>
</tr>
<tr>
<td>Netherlands (NL)</td>
<td>0(0-2)</td>
<td>0(0-1)</td>
<td>0.777</td>
<td>0.44</td>
</tr>
<tr>
<td>Xi-an (XI)</td>
<td>1(0-4)</td>
<td>1(0-4)</td>
<td>0.947</td>
<td>0.23</td>
</tr>
<tr>
<td>Japan (JP)</td>
<td>3(1-4)</td>
<td>0(0-4)</td>
<td>0.801</td>
<td>0.39</td>
</tr>
<tr>
<td>Finland (FI)</td>
<td>0(0-1)</td>
<td>0(0-1)</td>
<td>0.834</td>
<td>0.34</td>
</tr>
<tr>
<td>Germany (GE)</td>
<td>0(0-1)</td>
<td>0(0-0)</td>
<td>0.870</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* Spearman's \( r \) rank correlation between antrum score for atrophy and for intestinal metaplasia; all values except New Orleans significant.

† Increase in antrum atrophy score per 10 years age increase.
Fig 3. Correlation between antrum atrophy and gastric cancer prevalence

Fig 4. Correlation between antrum intestinal metaplasia and gastric cancer prevalence